

Application No.: 10/617,489

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AMENDMENTS TO THE CLAIMS

1. (Withdrawn): An isolated antibody that specifically binds to an N-terminal sequence of whole parathyroid hormone (PTH) and is capable of detecting said whole PTH at a physiological level in a mammalian sample, with a proviso that said isolated antibody avoids binding to a non-whole PTH fragment.
2. (Withdrawn): The isolated antibody of claim 1, which is a monoclonal or polyclonal antibody or antibody fragment.
3. (Withdrawn): The isolated antibody of claim 1, which specifically binds to an epitope comprised in PTH₁₋₆, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₂, PTH₁₋₁₅ or PTH₃₋₁₂.
4. (Withdrawn): The isolated antibody of claim 1, which specifically binds to the parathyroid hormone peptide human PTH₁₋₈, rat PTH₁₋₈, mouse PTH₁₋₈, bovine PTH₁₋₈, canine PTH₁₋₈, porcine PTH₁₋₈, horse PTH₁₋₈, human PTH₁₋₁₅, rat PTH₁₋₁₅, mouse PTH₁₋₁₅, bovine PTH₁₋₁₅, canine PTH₁₋₁₅, porcine PTH₁₋₁₅, or horse PTH₁₋₁₅, wherein at least four amino acids in said peptide sequence are part of a reactive portion with the antibody.
5. (Withdrawn): The isolated antibody of claim 1, which specifically binds to an epitope comprised in PTH₁₋₅, PTH₁₋₇, PTH₁₋₈, PTH₁₋₁₀, PTH₁₋₁₁, PTH₁₋₁₃, PTH₁₋₁₄, PTH₁₋₁₅, PTH₁₋₁₆, PTH₁₋₁₇, PTH₁₋₁₈, PTH₁₋₁₉, PTH₁₋₂₀, PTH₁₋₂₁, PTH₁₋₂₂, PTH₁₋₂₃, PTH₁₋₂₄, PTH₁₋₂₅, PTH₁₋₂₆, hPTH₁₋₂₇, PTH₁₋₂₈, PTH₁₋₂₉, PTH₁₋₃₀, PTH₁₋₃₁, PTH₁₋₃₂, PTH₁₋₃₃, PTH₁₋₃₄, PTH₁₋₃₅, PTH₁₋₃₆, PTH₁₋₃₇, PTH₂₋₅, PTH₂₋₆, PTH₂₋₇, PTH₂₋₈, PTH₂₋₉, PTH₂₋₁₀, PTH₂₋₁₁, PTH₂₋₁₂, PTH₂₋₁₃, PTH₂₋₁₄, PTH₂₋₁₅, PTH₂₋₁₆, PTH₂₋₁₇, PTH₂₋₁₈, PTH₂₋₁₉, PTH₂₋₂₀, PTH₂₋₂₁, PTH₂₋₂₂, PTH₂₋₂₃, PTH₂₋₂₄, PTH₂₋₂₅, PTH₂₋₂₆, PTH₂₋₂₇, PTH₂₋₂₈, PTH₂₋₂₉, PTH₂₋₃₀, PTH₂₋₃₁, PTH₂₋₃₂, PTH₂₋₃₃, PTH₂₋₃₄, PTH₂₋₃₅, PTH₂₋₃₆, PTH₂₋₃₇, PTH₃₋₆, PTH₃₋₇, PTH₃₋₈, PTH₃₋₉, PTH₃₋₁₀, PTH₃₋₁₁, PTH₃₋₁₃, PTH₃₋₁₄, PTH₃₋₁₅, PTH₃₋₁₆, PTH₃₋₁₇, PTH₃₋₁₈, PTH₃₋₁₉, PTH₃₋₂₀, PTH₃₋₂₁, PTH₃₋₂₂, PTH₃₋₂₃, PTH₃₋₂₄, PTH₃₋₂₅, PTH₃₋₂₆, PTH₃₋₂₇, PTH₃₋₂₈, PTH₃₋₂₉, PTH₃₋₃₀, PTH₃₋₃₁, PTH₃₋₃₂, PTH₃₋₃₃, PTH₃₋₃₄, PTH₃₋₃₅, PTH₃₋₃₆, PTH₃₋₃₇, PTH₄₋₇, PTH₄₋₈, PTH₄₋₉, PTH₄₋₁₀, PTH₄₋₁₁, PTH₄₋₁₂, PTH₄₋₁₃, PTH₄₋₁₄, PTH₄₋₁₅, PTH₄₋₁₆, PTH₄₋₁₇, PTH₄₋₁₈, PTH₄₋₁₉, PTH₄₋₂₀,

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c) assessing a complex formed between said whole parathyroid hormone, if present in said sample, and said antibody, to measure physiological level of said whole parathyroid hormone in said mammalian sample.

11. (Original): The method of claim 10, wherein the sample is selected from the group consisting of a serum, a plasma and a blood sample.

12. (Original): The method of claim 10, wherein the sample is a clinical sample.

13. (Original): The method of claim 10 which is used for clinical management of renal disease subjects, subjects afflicted with osteoporosis or diagnosing primary hyperparathyroidism.

14. (Original): The method of claim 10, wherein the mammal is a human.

15. (Original): The method of claim 14, wherein the sample is a human clinical sample.

16. (Original): The method of claim 10, wherein the antibody is a monoclonal or polyclonal antibody or antibody fragment.

17. (Previously Presented): The method of claim 10, wherein the antibody specifically binds to an epitope comprised in PTH₁₋₆, PTH₁₋₈, PTH₁₋₉, PTH₁₋₁₂, or PTH₁₋₁₅.

18. (Original): The method of claim 10, wherein the antibody specifically binds to the parathyroid hormone peptide human PTH₁₋₈, rat PTH₁₋₈, mouse PTH₁₋₈, bovine PTH₁₋₈, canine PTH₁₋₈, porcine PTH₁₋₈, horse PTH₁₋₈, human PTH₁₋₁₅, rat PTH₁₋₁₅, mouse PTH₁₋₁₅, bovine PTH₁₋₁₅, canine PTH₁₋₁₅, porcine PTH₁₋₁₅, or horse PTH₁₋₁₅, wherein at least four amino acids in said peptide sequence are part of a reactive portion with the antibody.

19. – 21. (Canceled):

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22. (Previously Presented): The method of claim 10, wherein the non-whole PTH fragment is selected from the group consisting of PTH₃₋₈₄, PTH₄₋₈₄, PTH₅₋₈₄, PTH₆₋₈₄, PTH₇₋₈₄, PTH₈₋₈₄, PTH₉₋₈₄, PTH₁₀₋₈₄, PTH₁₁₋₈₄, PTH₁₂₋₈₄, PTH₁₃₋₈₄, PTH₁₄₋₈₄, PTH₁₅₋₈₄, PTH₁₆₋₈₄, PTH₁₇₋₈₄, PTH₁₈₋₈₄, PTH₁₉₋₈₄, PTH₂₀₋₈₄, PTH₂₁₋₈₄, PTH₂₂₋₈₄, PTH₂₃₋₈₄, PTH₂₄₋₈₄, PTH₂₅₋₈₄, PTH₂₆₋₈₄, PTH₂₇₋₈₄, PTH₂₈₋₈₄, PTH₂₉₋₈₄, PTH₃₀₋₈₄, PTH₃₁₋₈₄, PTH₃₂₋₈₄, PTH₃₃₋₈₄ and PTH₃₄₋₈₄.

23. (Original): The method of claim 10, wherein the non-whole PTH fragment is a peptide having an amino acid sequence of human PTH₇₋₈₄.

24. (Original): The method of claim 10, wherein the complex is assessed by a sandwich or competitive assay format.

25. (Original): The method of claim 24, wherein the antibody that specifically binds to an N-terminal sequence of whole PTH is used as a first antibody and an antibody that is capable of binding to a portion of whole PTH other than the N-terminal sequence which binds to the first antibody is used as a second antibody in a sandwich assay format.

26. (Original): The method of claim 25, wherein either the first antibody or the second antibody is attached to a surface and functions as a capture antibody.

27. (Currently Amended): The method of claim 26, wherein the capture antibody is attached to the surface directly ~~or indirectly~~.

28. (Original): The method of claim 26, wherein the capture antibody is attached to the surface via a biotin-avidin (or streptavidin) linking pair.

29. (Original): The method of claim 10, wherein the complex is assessed by a format selected from the group consisting of an enzyme-linked immunosorbent assay (ELISA), immunoblotting, immunoprecipitation, radioimmunoassay (RIA), immunostaining, latex agglutination, indirect hemagglutination assay (IHA), complement fixation, indirect

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immunofluorescent assay (IFA), nephelometry, flow cytometry assay, plasmon resonance assay, chemiluminescence assay, lateral flow immunoassay, u-capture assay, inhibition assay and avidity assay.

30. (Currently Amended): The method of claim 10, wherein the complex is assessed in a homogeneous or a heterogeneous assay format.

31. (Original): The method of claim 10, wherein the physiological level of whole parathyroid hormone is less than 4 pmol/L.

32. (Original): The method of claim 10, wherein the physiological level of whole parathyroid hormone is from about 0.2 pmol/L to about 4 pmol/L.

33. (Original): The method of claim 10, which further comprises measuring a PTH peptide fragment level and/or total PTH level.

34. (Original): The method of claim 33, wherein said sample is contacted with one or more isolated antibodies, and wherein each of said one or more isolated antibodies specifically bind one or more PTH peptide fragments selected from the group consisting of: PTH₃₉₋₈₄, PTH₁₋₃₄, PTH₄₃₋₆₈, PTH₇₋₈₄, PTH₃₉₋₆₈, PTH₅₃₋₈₄, PTH₆₅₋₈₄, PTH₄₄₋₆₈, PTH₁₉₋₈₄, PTH₂₃₋₈₄, PTH₁₋₃₈, PTH₁₋₄₈, PTH₁₋₅₈, PTH₁₋₆₈, and PTH₁₋₇₈.

35. (Original): The method of claim 33, which further comprises comparing at least two parameters selected from the group consisting of the whole PTH level, total PTH peptide fragment level, total PTH level, C-terminal PTH fragment (cPTH) level, N-terminal PTH fragment level, and mid-terminal PTH fragment (mPTH) level.

36. (Original): The method of claim 35, wherein the results of said comparison are used to determine whether the mammal suffers from a bone turnover related disorder, or to monitor bone disease or disorder related treatment.

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37. (Original): The method of claim 36, which is used in the diagnosis or monitoring of treatment for adynamic bone disease (ADN) or severe hyperparathyroidism.

38. (Original): The method of claim 35, wherein the comparison is in the form of a ratio or proportion between the whole PTH level and the total PTH level.

39. (Original): The method of claim 35, wherein the comparison is in the form of a ratio or proportion between the whole PTH level versus the combined total of the total PTH level minus the whole PTH level.

40. – 57. (Canceled)

58. (Original): The method of claim 10, which is used for:

- a) differentiating between a person having substantially normal parathyroid function and having hyperparathyroidism;
- b) monitoring parathyroid related bone disease and treatment;
- c) monitoring effects of therapeutic treatment for hyperparathyroidism; or
- d) diagnosing parathyroid related bone disease.

59. (Previously Presented): A kit for measuring a physiological level of whole parathyroid hormone in a mammalian sample, which kit comprises, in a container, an isolated antibody that specifically binds to an N-terminal sequence of whole parathyroid hormone (PTH) and is capable of detecting said whole PTH at a physiological level in a mammalian sample, with a proviso that said isolated antibody avoids binding to a non-whole PTH fragment in said sample.

60. (Withdrawn): An isolated parathyroid hormone (PTH) peptide, which is selected from the group consisting of PTH₁₋₁₁, PTH₁₋₁₃, PTH₁₋₁₄, PTH₁₋₁₅, PTH₁₋₁₆, PTH₁₋₁₇, PTH₁₋₁₈, PTH₁₋₁₉, PTH₁₋₂₀, PTH₁₋₂₁, PTH₁₋₂₂, PTH₁₋₂₃, PTH₁₋₂₄, PTH₁₋₂₅, PTH₁₋₂₆, hPTH₁₋₂₇, PTH₁₋₂₈, PTH₁₋₂₉, PTH₁₋₃₀, PTH₁₋₃₁, PTH₁₋₃₂, PTH₁₋₃₃, PTH₁₋₃₄, PTH₁₋₃₅, PTH₁₋₃₆, PTH₂₋₅, PTH₂₋₆, PTH₂₋₈, PTH₂₋₉, PTH₂₋₁₀, PTH₂₋₁₁, PTH₂₋₁₂, PTH₂₋₁₃, PTH₂₋₁₄, PTH₂₋₁₅, PTH₂₋₁₆, PTH₂₋₁₇, PTH₂₋₁₈, PTH₂₋₁₉, PTH₂₋₂₀, PTH₂₋₂₁,

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PTH₂₋₂₂, PTH₂₋₂₃, PTH₂₋₂₄, PTH₂₋₂₅, PTH₂₋₂₆, PTH₂₋₂₇, PTH₂₋₂₈, PTH₂₋₂₉, PTH₂₋₃₀, PTH₂₋₃₁, PTH₂₋₃₂, PTH₂₋₃₃, PTH₂₋₃₄, PTH₂₋₃₅, PTH₂₋₃₆, PTH₃₋₆, PTH₃₋₇, PTH₃₋₉, PTH₃₋₁₀, PTH₃₋₁₁, PTH₃₋₁₂, PTH₃₋₁₃, PTH₃₋₁₄, PTH₃₋₁₅, PTH₃₋₁₆, PTH₃₋₁₇, PTH₃₋₁₈, PTH₃₋₁₉, PTH₃₋₂₀, PTH₃₋₂₁, PTH₃₋₂₂, PTH₃₋₂₃, PTH₃₋₂₄, PTH₃₋₂₅, PTH₃₋₂₆, PTH₃₋₂₇, PTH₃₋₂₈, PTH₃₋₂₉, PTH₃₋₃₀, PTH₃₋₃₁, PTH₃₋₃₂, PTH₃₋₃₃, PTH₃₋₃₄, PTH₃₋₃₅, PTH₃₋₃₆, PTH₄₋₇, PTH₄₋₈, PTH₄₋₉, PTH₄₋₁₀, PTH₄₋₁₁, PTH₄₋₁₃, PTH₄₋₁₄, PTH₄₋₁₅, PTH₄₋₁₆, PTH₄₋₁₇, PTH₄₋₁₈, PTH₄₋₁₉, PTH₄₋₂₀, PTH₄₋₂₁, PTH₄₋₂₂, PTH₄₋₂₃, PTH₄₋₂₄, PTH₄₋₂₅, PTH₄₋₂₆, PTH₄₋₂₇, PTH₄₋₂₈, PTH₄₋₂₉, PTH₄₋₃₀, PTH₄₋₃₁, PTH₄₋₃₂, PTH₄₋₃₃, PTH₄₋₃₄, PTH₄₋₃₅, PTH₄₋₃₆, PTH₅₋₈, PTH₅₋₉, PTH₅₋₁₁, PTH₅₋₁₂, PTH₅₋₁₃, PTH₅₋₁₄, PTH₅₋₁₅, PTH₅₋₁₆, PTH₅₋₁₇, PTH₅₋₁₈, PTH₅₋₁₉, PTH₅₋₂₀, PTH₅₋₂₁, PTH₅₋₂₂, PTH₅₋₂₃, PTH₅₋₂₄, PTH₅₋₂₅, PTH₅₋₂₆, PTH₅₋₂₇, PTH₅₋₂₈, PTH₅₋₂₉, PTH₅₋₃₀, PTH₅₋₃₁, PTH₅₋₃₂, PTH₅₋₃₃, PTH₅₋₃₄, PTH₅₋₃₅, PTH₅₋₃₆, and PTH₅₋₃₇.

61. (Withdrawn): The isolated PTH peptide of claim 60, which is conjugated to a carrier to enhance the PTH peptide's immunogenicity.

62. (Withdrawn): The isolated PTH peptide of claim 61, wherein the carrier is a carrier protein.

63. (Withdrawn): The isolated PTH peptide of claim 62, wherein the PTH peptide and the carrier protein are parts of a fusion protein.

64. (Withdrawn): An immunogen, which immunogen comprises:

- a) a PTH peptide of claim 60; and
- b) an immune response potentiator.

65. (Withdrawn): The immunogen of claim 64, wherein the immune response potentiator is selected from the group consisting of Bacille Calmette-Guerin (BCG), *Corynebacterium Parvum*, *Brucella abortus* extract, glucan, levamisole, tilorone, an enzyme and a non-virulent virus.

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- b) means for introducing said isolated PTH peptide to a mammal in an amount sufficient to produce an antibody to said PTH peptide; and
- c) means for recovering said antibody from said mammal.

75. (Withdrawn): A method for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which method comprises:

- a) introducing a MAP of claim 66 to a mammal in an amount sufficient to produce an antibody to a PTH peptide comprised in said MAP; and
- b) recovering said antibody from said mammal.

76. (Withdrawn): An antibody to a PTH or a PTH peptide produced by the method of claim 75.

77. (Withdrawn): A kit for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which kit comprises:

- a) a MAP of claim 66;
- b) means for introducing said MAP to a mammal in an amount sufficient to produce an antibody to a PTH peptide comprised in said MAP; and
- c) means for recovering said antibody from said mammal.

78. (Withdrawn): A method for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which method comprises:

- a) introducing a PTH protein or peptide from between PTH₁₋₃₄ and PTH₁₋₈₄ to a mammal in an amount sufficient to produce an antibody to said PTH protein or peptide;
- b) recovering said antibody from said mammal; and
- c) affinity purifying a PTH antibody that specifically binds to an epitope comprised in a PTH peptide of claim 60 using said PTH peptide.

79. (Withdrawn): An antibody to a PTH or a PTH peptide produced by the method of claim 78.

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66. (Withdrawn): A multiple antigenic peptide (MAP), which MAP comprises a branched oligolysine core conjugated with a plurality of the PTH peptide of claim 60.

67. (Withdrawn): The MAP of claim 66, wherein the branched oligolysine core comprises 3, 7 or 15 lysine residues.

68. (Withdrawn): The MAP of claim 66, wherein the plurality of the PTH peptide is conjugated to the branched oligolysine core via a spacer.

69. (Withdrawn): The MAP of claim 68, wherein the spacer is an amino acid residue.

70. (Withdrawn): The MAP of claim 68, which comprises 4, 8 or 16 copies of the PTH peptide.

71. (Withdrawn): The MAP of claim 66, wherein the plurality of the PTH peptide comprises same or different PTH peptides.

72. (Withdrawn): A method for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which method comprises:

- a) introducing an isolated PTH peptide of claim 60 to a mammal in an amount sufficient to produce an antibody to said PTH peptide; and
- b) recovering said antibody from said mammal.

73. (Withdrawn): An antibody to a PTH or a PTH peptide produced by the method of claim 72.

74. (Withdrawn): A kit for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which kit comprises:

- a) an isolated PTH peptide of claim 60;

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80. (Withdrawn): A kit for producing an antibody to a parathyroid hormone (PTH) or a PTH peptide, which kit comprises:

- a) a PTH protein or peptide from between PTH₁₋₃₄ and PTH₁₋₈₄;
- b) means for introducing said PTH protein or peptide from between PTH₁₋₃₄ and PTH₁₋₈₄ to a mammal in an amount sufficient to produce an antibody to said PTH protein or peptide;
- c) means for recovering said antibody from said mammal; and
- d) a PTH peptide of claim 60.

81. (Previously Presented): The method of claim 10, wherein the physiological level of whole parathyroid hormone is from about 7 pm/ml to about 39 pm/ml.

82. (New): The method of claim 26, wherein the capture antibody is attached to the surface indirectly.

83. (New): The method of claim 10, wherein the complex is assessed in a heterogeneous assay format.